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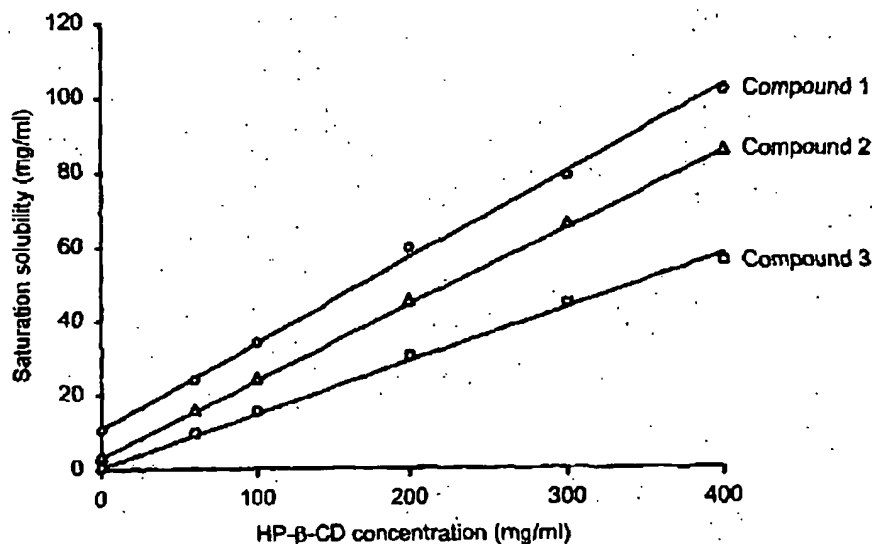
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(54) Title: OPTHALMIC ANTIBIOTIC DRUG FORMULATIONS CONTAINING A CYCLODEXTRIN COMPOUND AND  
CETYL PYRIDINIUM CHLORIDE



(57) Abstract: There is provided a pharmaceutical composition suitable for topical administration to an eye, the composition comprising (a) an antibiotic drug, for example linezolid, in a therapeutically or prophylactically effective drug concentration, (b) as a solubilizing agent, a pharmaceutically acceptable cyclodextrin compound in a concentration sufficient to maintain the drug in solution at such a drug concentration, and (c) as a preservative, cetyl pyridinium chloride. The composition is particularly useful for the treatment and/or prevention of eye infections due to gram positive bacteria.

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OPHTHALMIC ANTIBIOTIC DRUG  
FORMULATIONS CONTAINING A CYCLODEXTRIN COMPOUND  
AND CETYL PYRIDINIUM CHLORIDE

This application claims the benefit of United States Provisional Application  
5 Number 60/358,760, filed February 22, 2002.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition in an aqueous  
solution form useful for administration to an eye of a subject for treatment or  
prevention of infectious disease therein. In particular, the present invention relates to  
10 such a composition having as an active agent an antibiotic drug, as a solubilizing agent  
a cyclodextrin compound, and as a preservative a quaternary ammonium compound  
that does not inhibit solubilization of the antibiotic drug by the cyclodextrin compound.  
The field of the present invention also includes therapeutic or prophylactic use of such  
a composition.

15 BACKGROUND OF THE INVENTION

Many different antibiotic drugs have been included in formulations designed for  
oral, parenteral, and topical administration, including formulations for ophthalmic  
administration.

Numerous oxazolidinone compounds have been reported as having  
20 therapeutically and/or prophylactically useful antibiotic or antimicrobial, in particular  
an antibacterial, effect. Among such compounds are those illustratively disclosed in  
the following patents, each of which is individually incorporated herein by reference.

U.S. Patent No. 5,164,510 to Brickner.

U.S. Patent No. 5,231,188 to Brickner.

25 U.S. Patent No. 5,565,571 to Barbachyn & Brickner.

U.S. Patent No. 5,627,181 to Riedl *et al.*

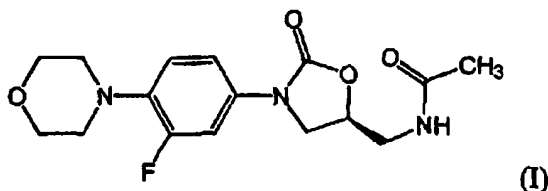
U.S. Patent No. 5,652,238 to Barbachyn *et al.*

U.S. Patent No. 5,688,792 to Barbachyn *et al.*

U.S. Patent No. 5,698,574 to Riedl *et al.*

30 U.S. Patent No. 6,069,145 to Betts.

Compounds disclosed in above-cited U.S. Patent No. 5,688,792 include for example the compound (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, referred to herein as "linezolid." Linezolid has the structure shown in formula (I):



5 and is in commercial use as a medicament under the trademark Zyvox® of Pharmacia Corporation. Linezolid exhibits strong antibacterial activity against gram-positive organisms including those of the following genera: *Staphylococcus* (e.g., *Staphylococcus aureus*, *Staphylococcus epidermidis*), *Streptococcus* (e.g., *Streptococcus viridans*, *Streptococcus pneumoniae*), *Enterococcus* (e.g., *Enterococcus fecalis*, *Enterococcus faecium*), *Bacillus*, *Corynebacterium*, *Chlamydia* and *Neisseria*. Many such gram-positive organisms have developed significant levels of resistance to other antibiotics. Oxazolidinone antibiotics are also generally effective against anaerobic organisms such as those of the genera *Bacteroides* and *Clostridia*, and  
10 against acid-fast organisms such as those of the genus *Mycobacterium*.

Above-cited U.S. Patent No. 5,688,792 discloses that antibiotic oxazolidinone compounds, including linezolid, can be formulated as a gel or cream for topical application to skin.

Many antibiotic compounds, including oxazolidinone compounds useful as  
20 antibiotics, do not form, or do not readily form, salts. For these compounds, and where for any reason it is preferred not to provide the antibiotic in salt form, it is generally difficult to formulate the antibiotic as a solution in a pharmaceutically acceptable liquid carrier, particularly an aqueous carrier. Most such compounds have relatively low solubility in water. In the case of linezolid, for example, the solubility at  
25 ambient temperature is less than 3 mg/ml and the practical limit of concentration in aqueous solution is about 2 mg/ml.

Where ophthalmic administration of an oxazolidinone antibiotic drug is contemplated, it is desired to achieve sufficiently high concentrations of the drug to be therapeutically effective in treating eye infections while ensuring all or substantially all

of the drug is in solution. Undissolved, particulate, forms of any ingredient of an ophthalmic solution can cause eye irritation, upon administration to the eye of a subject. Some have approached the problem of a need to administer drugs with low solubility to an eye by providing sufficiently dilute aqueous ophthalmic solutions of a poorly soluble drug to ensure that the drug is in solution. Such dilute solutions of drug must be administered to an eye more frequently than would a higher concentration solution of the same drug, were it possible to make such a solution.

Use of dilute solutions of oxazolidinones is disclosed in U.S. Patent No. 6,337,329 B1 (International counterpart published as WO 00/03710), incorporated herein by reference. The patent, specifically, discloses a method of treating bacterial keratitis or bacterial conjunctivitis in an eye, comprising topical administration of an oxazolidinone antibiotic to the infected eye. Preferred oxazolidinone compounds for use according to the method of WO 00/03710 include (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (linezolid) and (S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (eperezolid). The oxazolidinone compound is said to be administered in a formulation such as a solution, cream, ointment, emulsion, suspension or slow release formulation, a solution being preferred. Ophthalmic formulations exemplified therein include 10% and 12% weight/volume solutions of linezolid. At such low concentrations of linezolid, it is further disclosed in U.S. Patent No. 6,337,329 B1 that the oxazolidinone compound can be used individually, in combination with another oxazolidinone compound, in combination with other antibacterial agents, or in combination with non-antibacterial agents.

International Patent Publication No. WO 00/18387, incorporated herein by reference, discloses additional dilute aqueous ophthalmic compositions comprising an oxazolidinone antimicrobial agent. Preferred oxazolidinone compounds according to WO 00/18387 are those of above-cited U.S. Patent No. 5,627,181. The oxazolidinone component of the compositions was disclosed to typically be present in a concentration of from about 0.1 to about 1.0 percent by weight of the composition (p. 8). The international patent publication also disclosed that the compositions can further comprise an anti-inflammatory agent.

Where ophthalmic administration of an oxazolidinone antibiotic drug is

contemplated, it is desired to be able to administer a pharmaceutically effective dose in as small a volume as possible, without having anything in the ophthalmic solution likely to irritate the eye. It will readily be understood that it is difficult to achieve such concentrations by administration of a relatively small volume of a composition wherein the drug is present in dissolved form, unless the composition has a relatively high drug loading, and in particular a drug loading substantially above the limit of solubility in water of most oxazolidinone antibiotics not in the form of a salt.

Derivatives of cyclodextrin, including  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrins and derivatives thereof, such as ether and mixed ether derivatives, and derivatives bearing sugar residues have been disclosed as being suitable for use in the solubilization of various drugs that are only sparingly soluble in water. EP 0149 197 B2 (Canadian counterpart, CA 1222697) discloses the suitability of partially etherified  $\beta$ -cyclodextrin and derivatives thereof, including hydroxyethyl, hydroxypropyl, and hydroxypropyl-methyl- $\beta$  cyclodextrin for the solubilization of various types of drugs which are instable or only sparingly soluble in water. None of the drugs disclosed by EP 0149 197 B2 as having been solubilized with one or more of the partially etherified  $\beta$ -cyclodextrins was an antibiotic, much less an oxazolidinone. Likewise, U.S. Patent No. 4,727,064 discloses the use of hydroxypropyl- $\beta$ -cyclodextrin and the use of mixtures of that cyclodextrin derivative, diethylaminoethyl- $\beta$ -cyclodextrin, carboxymethyl- $\beta$ -cyclodextrin, and carboxamidomethyl- $\beta$ -cyclodextrin to assist in the dissolution of drugs, but does not disclose the solubilization of any oxazolidinone using such a solubility enhancer. Various sulfoalkyl ether cyclodextrin derivatives, including sulfobutylether- $\beta$ -cyclodextrin, and their utility in solubilizing certain active agents are disclosed in U.S. Patent No.'s 5,134,127; 5,376,645. Uses of such sulfoalkyl ether cyclodextrin derivatives in solubilizing additional active agents are disclosed in U.S. Patent No.'s 5,134,127, 5,874,418; 6,046,177; and 6,133,248.

Multi-dose formulations, including ophthalmic formulations, typically contain preservatives in order to maintain sterility after opening and during use. U.S. Patent No. 5,985,310 notes problems with cyclodextrins inactivating the antimicrobial activity of quaternary ammonium compounds and other preservatives pharmaceutical compositions containing cyclodextrins. That patent discloses the use of certain

preservatives, including benzalkonium halide compounds, polymeric quaternary ammonium compounds, and quaternary ammonium alkylene glycol phospholipid derivatives that do not interact with cyclodextrins in a way that significantly reduces or eliminates their antimicrobial preservative activity in a solution containing  
5 cyclodextrins.

WO 97/10805 notes a similar negative impact of cyclodextrins on quaternary ammonium salt preservatives in aqueous ophthalmic solutions. WO 97/10805 discloses a means of eliminating this negative impact on such preservatives by including an alkylene glycol in aqueous ophthalmic solutions containing cyclodextrin or  
10 a cyclodextrin derivative, and a quaternary ammonium salt preservative. Many different drugs are listed as being suitable for use in such formulations; however, none are antibiotics, much less oxazolidinone antibiotic drugs.

The references above indicate that cyclodextrins and derivatives thereof can be suitable for solubilization of a variety of different drugs with low solubility. The  
15 references summarized above also indicate that when preservatives, particularly quaternary ammonium salts, are included in solutions containing cyclodextrins the preservatives interact with the cyclodextrins in such a way as to inhibit the effectiveness of the preservatives. Even preservatives or preservative systems that do not react with the cyclodextrin component of such a formulation could react with an  
20 eye upon administration, or with other components of the formulation. None of the references described above disclose any formulation of an oxazolidinone antibiotic drug and a cyclodextrin compound, much less such an oxazolidinone formulation suitable for ophthalmic delivery.

A need, therefore, exists for a solution composition of an oxazolidinone  
25 antibiotic drug having a drug loading substantially in excess of the practical limit of solubility of the drug in water. A particular need exists for an ophthalmically deliverable solution composition of an antibiotic drug with low solubility in water, wherein the composition comprises a relatively high concentration of the drug and a solubilization agent, such as a cyclodextrin or derivative thereof, with a preservative  
30 that preserves the effectiveness of the antibiotic while not interfering with the solubilizing effect of the cyclodextrin compound in the solution. These and other needs will be seen to be met by the invention now described.

The present preservative system meets the needs discussed above, as becomes apparent from the description and illustration of the present invention, below.

### SUMMARY OF THE INVENTION

Although the description of the compositions and methods of the present invention set forth herein, below, is directed toward ophthalmic antibiotic compositions and applications, it is contemplated that the present invention would also apply to compositions for other forms of topical delivery, as well as for oral and parenteral administration.

The present invention provides a pharmaceutical composition suitable for topical administration to an eye, the composition comprising: (a) an antibiotic drug, in a concentration effective for treatment or prophylaxis of a bacterial infection of at least one tissue of the eye, (b) a pharmaceutically acceptable cyclodextrin compound in a cyclodextrin concentration sufficient to maintain the drug in solution at the drug concentration, and (c) cetyl pyridinium chloride.

The reason for including cyclodextrin is again not a restriction for the practice of this invention. It can be for solubilization, reduction of irritation, permeation enhancement, and stability enhancement. It is believed, without being bound by theory, that the enhanced solubility of the oxazolidinone drug in a composition of the invention is due to association of at least a portion of the drug with the cyclodextrin. It is further believed that at least one mechanism by which the drug associates with the cyclodextrin compound to enhance solubility of the drug in an aqueous medium is through formation of an inclusion complex. Such complexes or conjugates are known in the art to form with a variety of drugs, and a number of advantages have been postulated for use of cyclodextrin-drug complexes in pharmacy. See for example review articles by Bekers *et al.* (1991) in *Drug Development and Industrial Pharmacy* 17: 1503-1549; Szejtli (1994) in *Medical Research Reviews* 14: 353-386; and Zhang & Rees (1999) in *Expert Opinion on Therapeutic Patents* 9: 1697-1717.

Formulations of various drugs with various cyclodextrins have been proposed in the patent literature, including the patents and publications referenced below.

U.S. Patent No. 5,670,530 to Chen & Shishido discloses compositions comprising a rhodacyanine anti-cancer agent and a cyclodextrin.



U.S. Patent No. 5,756,546 to Pirotte *et al.* discloses compositions comprising nimesulide and a cyclodextrin.

U.S. Patent No. 5,807,895 to Stratton *et al.* discloses compositions comprising a prostaglandin and a cyclodextrin.

5 U.S. Patent No. 5,824,668 to Rubinfeld *et al.* discloses compositions comprising a  $5\beta$  steroid drug and a cyclodextrin.

International Patent Publication No. WO 96/32135 discloses compositions comprising propofol and a cyclodextrin.

10 International Patent Publication No. WO 96/38175 discloses compositions comprising an antiulcerative benzimidazole compound and a branched cyclodextrin-carboxylic acid.

International Patent Publication No. WO 97/39770 discloses compositions comprising a thrombin inhibitor and a cyclodextrin.

15 International Patent Publication No. WO 98/37884 discloses compositions comprising a 3,4-diarylchroman compound and a cyclodextrin.

International Patent Publication No. WO 98/55148 discloses compositions comprising a sparingly water-soluble drug, a cyclodextrin, a water-soluble acid and a water-soluble organic polymer.

20 International Patent Publication No. WO 98/58677 discloses compositions comprising voriconazole and a cyclodextrin.

International Patent Publication No. WO 99/24073 discloses compositions comprising a taxoid such as paclitaxel or docetaxel and a cyclodextrin.

International Patent Publication No. WO 99/27932 discloses compositions comprising an antifungal compound of defined formula and a cyclodextrin.

25 However, the degree of enhancement of solubility achievable through complexation with cyclodextrins of a particular drug or class of drugs is not generally predictable. Cyclodextrins are expensive excipients and in many cases the degree of enhancement of solubility, or other benefit obtained, has not economically justified the increased cost of a formulation arising from addition of a cyclodextrin. The present  
30 invention is based in part on the discovery that addition of a relatively modest amount of a cyclodextrin compound, in a preservative free solution, increases the solubility of an oxazolidinone antibiotic drug to a surprising degree. This enhancement in

solubility, among other benefits, makes it possible for the first time to ophthalmically deliver a therapeutically or prophylactically effective dose of the oxazolidinone in a minimal number of doses.

Many different preservatives and preservative systems have been discovered  
5 and developed that are suitable for use in ophthalmic applications. However, many such preservatives and preservative systems are unsuitable for use in ophthalmic formulations containing an active agent and a cyclodextrin compound, as they tend to interfere with or even prevent the solubilization of the active agent by the cyclodextrin. Furrer *et al.*, *European J. of Pharmaceutics and Biopharmaceutics* 47:105-112 (1999).  
10 Alternative, synthetic preservatives have been developed, such as the polymeric forms of cetyl pyridinium chloride, disclosed by U.S. Patent No. 5,985,310, discussed above, that minimize the degree of such inhibitory interaction between a preservative and a cyclodextrin compound. Others have included components, such as an alkylene glycol, in order to inhibit any such interaction between a preservative, such as a quaternary  
15 ammonium salt, and cyclodextrins. Both approaches involve modifications and additions to the composition found herein to be unnecessary.

It is unpredictable to select an ophthalmically compatible preservative for a given drug or class of drugs that will not inhibit solubilization of the drug by a cyclodextrin compound. Given the teaching of a need to modify or inhibit the binding  
20 of quaternary ammonium salts in the prior art, e.g. U.S. Patent No. 5,985,310 and WO 97/10805, it is surprising and unexpected that cetyl pyridinium chloride, a quaternary ammonium salt, can be used without any such modification in a ophthalmic composition of an oxazolidinone antimicrobial drug and a cyclodextrin compound, and not inhibit solubilization of the drug by the cyclodextrin.

25 The term "pharmaceutically acceptable" in relation to a cyclodextrin or other excipient herein means having no persistent detrimental effect on the eye or general health of the subject being treated. The pharmaceutical acceptability of a cyclodextrin depends, among other factors, on the particular cyclodextrin compound in question, on its concentration in the administered composition, and on the route of administration.  
30 For example, use of  $\beta$ -cyclodextrin as an excipient in intravenous compositions is limited by hemolytic and nephrotoxic effects, but is generally non-toxic when administered orally.

Except where the context demands otherwise, use of the singular herein will be understood to embrace the plural. For example, by indicating above that a composition of the invention comprises "an oxazolidinone antibiotic drug" and "a pharmaceutically acceptable cyclodextrin compound", it will be understood that the composition can contain one or more such drugs and one or more such cyclodextrin compounds.

In one embodiment, present invention provides a method of treating an existing bacterial infection in the eye of a subject, comprising ophthalmically administering a therapeutically effective dose of the pharmaceutical composition, as described above.

10 Infective diseases of the eye for which compositions and methods of the invention are useful include without limitation conjunctivitis, keratitis, blepharitis, blepharoconjunctivitis, orbital and preseptal cellulitis and endophthalmitis. In preferred methods the infected tissue is one that is directly bathed by the lacrimal fluid, as in conjunctivitis, keratitis, blepharitis and blepharoconjunctivitis.

15 In infective diseases of the eye where the causal organism is non-bacterial, there can be benefit in prophylactic use of a composition of the invention to control secondary bacterial infections. Examples of such situations include conjunctivitis and keratitis of viral etiology, *e.g.*, adenoviral conjunctivitis, molluscum contagiosum, herpes simplex conjunctivitis and keratitis, *etc.*, and fungal keratitis.

20 Prophylactic uses of a composition of the invention also include post-traumatic prophylaxis, especially post-surgical prophylaxis, and prophylaxis prior to ocular surgery.

What constitutes a "concentration effective for treatment and/or prophylaxis of a bacterial infection" depends, among other factors, on the particular oxazolidinone compound or compounds being administered; the residence time provided by the particular formulation of the active agent; the species, age and body weight of the subject; the particular ophthalmic condition for which treatment or prophylaxis is sought; and the severity of the condition. In the case of linezolid, an effective concentration in a composition of the invention for topical administration to an eye will

25 generally be found in the range from about 0.1 mg/ml to about 100 mg/ml, more typically about 0.5 mg/ml to about 80 mg/ml. For oxazolidinone compounds other than linezolid, an appropriate concentration range is one that is therapeutically

30

equivalent to the linezolid concentration range indicated above.

The term "practical limit of solubility" in relation to a drug, such as the oxazolidinone of the present formulations, means the highest concentration at which the drug can be formulated in solution without risk of precipitation or crystallization of the drug during the normal range of manufacturing, packaging, storage, handling and use conditions. Typically, the practical limit of solubility is considerably lower than the true solubility limit in a given aqueous medium, for example about 70% of the true solubility limit. Thus, illustratively, for a drug having a true solubility limit in a given aqueous medium of 2.9 mg/ml, the practical limit of solubility is likely to be about 2 mg/ml.

The term "ophthalmically acceptable" with respect to a formulation, composition or ingredient herein means having no persistent detrimental effect on the treated eye or the functioning thereof, or on the general health of the subject being treated. It will be recognized that transient effects such as minor irritation or a "stinging" sensation are common with topical ophthalmic administration of drugs and the existence of such transient effects is not inconsistent with the formulation, composition or ingredient in question being "ophthalmically acceptable" as herein defined. However, preferred formulations, compositions and ingredients are those that cause no substantial detrimental effect, even of a transient nature.

Contemplated compositions are highly effective in treating gram-positive bacterial infections of the eye. Without being bound by theory, it is believed the higher concentrations of solubilized oxazolidinone possible in the formulations of the present invention, facilitated by the presence of a cyclodextrin compound, and by the presence of a preservative that does not degrade or interfere with the cyclodextrin, enables one to deliver a higher amount of an oxazolidinone antibiotic drug to ophthalmic tissues where it is needed most than is possible with existing formulations. Thus, one could treat or prevent bacterial infections or other conditions of an eye cited by treating the eye according to the method of the present invention.

Other advantages of the present invention will become apparent from the following description of the invention and Examples, below.

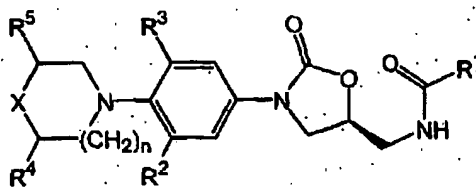
#### BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a graphical representation of data from the study described in Example

2 herein, and demonstrates enhanced saturation solubility of oxazolidinone compounds in aqueous solutions containing hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD).

### DETAILED DESCRIPTION OF THE INVENTION

Any antibiotic drug can be formulated with a cyclodextrin compound in accordance with the present invention. In one embodiment, the antibiotic drug is preferably present in the composition at a concentration above the practical limit of solubility of the drug in an aqueous solution at a physiologically compatible pH. In another embodiment, cyclodextrin improves stability of the active agent. In yet another embodiment, cyclodextrin improves penetration of the drug into the eye. In yet another embodiment, cyclodextrin improves ocular tolerance of the drug. The antibiotic is preferably an oxazolidinone antibiotic drug, *i.e.*, one having an oxazolidinone moiety as part of its chemical structure. In a preferred embodiment, the oxazolidinone drug is a compound of formula (II)



(II)

15 wherein:

R<sup>1</sup> is selected from (a) H, (b) C<sub>1-8</sub> alkyl optionally substituted with one or more F, Cl, OH, C<sub>1-8</sub> alkoxy, C<sub>1-8</sub> acyloxy or benzoxy groups, and including C<sub>3-6</sub> cycloalkyl, (c) amino, (d) mono- and di(C<sub>1-8</sub> alkyl)amino and (e) C<sub>1-8</sub> alkoxy groups;

20 R<sup>2</sup> and R<sup>3</sup> are independently selected from H, F and Cl groups;

R<sup>4</sup> is H or CH<sub>3</sub>;

R<sup>5</sup> is selected from H, CH<sub>3</sub>, CN, CO<sub>2</sub>R<sup>1</sup> and (CH<sub>2</sub>)<sub>m</sub>R<sup>6</sup> groups, where R<sup>1</sup> is as defined above, R<sup>6</sup> is selected from H, OH, OR<sup>1</sup>, OCOR<sup>1</sup>, NHCOR<sup>1</sup>, amino, mono- and di(C<sub>1-8</sub> alkyl)amino groups and m is 1 or 2;

25 n is 0, 1 or 2; and

X is O, S, SO, SO<sub>2</sub>, SNR<sup>7</sup> or S(O)NR<sup>7</sup> where R<sup>7</sup> is selected from H, C<sub>1-4</sub> alkyl (optionally substituted with one or more F, Cl, OH, C<sub>1-8</sub> alkoxy, amino, C<sub>1-8</sub> mono- or di(C<sub>1-8</sub> alkyl)amino groups), and p-toluenesulfonyl groups;

or a pharmaceutically acceptable salt thereof.

Particularly preferred oxazolidinone drugs according to this embodiment are compounds of formula (II) wherein  $R^1$  is  $CH_3$ ;  $R^2$  and  $R^3$  are independently selected from H and F but at least one of  $R^2$  and  $R^3$  is F;  $R^4$  and  $R^5$  are each H; n is 1; and X is O, S or  $SO_2$ . In another preferred embodiment, the oxazolidinone drug is selected

5 from linezolid, eperezolid, N-((5S)-3-(3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide, (S)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide, (S)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride and N-[[[(5S)-3-[4-(1,1-dioxido-4-

10 According to either of these preferred embodiments, an especially preferred oxazolidinone drug is linezolid. Another especially preferred oxazolidinone drug is N-[[[(5S)-3-[4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. The invention is illustrated herein with particular reference to linezolid, and it will be understood that any other oxazolidinone

15 antibacterial compound can, if desired, be substituted in whole or in part for linezolid, with appropriate adjustment in concentration and dosage ranges, in the compositions and methods herein described.

Oxazolidinone compounds used in compositions of the invention can be prepared by a process known *per se*, in the case of linezolid and eperezolid, for

20 example, by processes described in the following patents, each of which is individually incorporated herein by reference.

U.S. Patent No. 5,688,791.

U.S. Patent No. 5,837,870.

International Patent Publication No. WO 99/24393.

25 Other oxazolidinone drugs can be prepared by processes known *per se*, including processes set forth in patent publications disclosing such drugs.

The invention is illustrated herein with particular reference to linezolid, and it will be understood that any other oxazolidinone antimicrobial drug can, if desired, be substituted in whole or in part for linezolid, with appropriate adjustment in

30 concentration and dosage ranges, in the compositions and methods herein described.

Linezolid is usefully present in a composition of the invention at a concentration of about 3 mg/ml to as high a concentration as is practically enabled by

the cyclodextrin present therewith, for example about 100 mg/ml. However, in a composition intended for direct administration as formulated, the concentration of linezolid is preferably about 0.1 to about 100 mg/ml, more preferably about 0.5 to about 80 mg/ml, and even more preferably about 10 mg/ml to about 60 mg/ml for example about 50 mg/ml. Useful concentrations of other oxazolidinone drugs are those that are therapeutically equivalent to the linezolid concentration ranges given immediately above.

The cyclodextrin compound with which the oxazolidinone antibiotic drug is formulated according to the present invention is preferably selected from  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin,  $\gamma$ -cyclodextrin, alkylcyclodextrins (e.g., methyl- $\beta$ -cyclodextrin, dimethyl- $\beta$ -cyclodextrin, diethyl- $\beta$ -cyclodextrin), hydroxyalkylcyclodextrins (e.g., hydroxyethyl- $\beta$ -cyclodextrin, hydroxypropyl- $\beta$ -cyclodextrin), carboxyalkylcyclodextrins (e.g., carboxymethyl- $\beta$ -cyclodextrin) and sulfoalkylether cyclodextrins (e.g., sulfobutylether- $\beta$ -cyclodextrin). More preferred are hydroxyalkyl- $\beta$ -cyclodextrins and sulfoalkylether- $\beta$ -cyclodextrins; still more preferred are hydroxypropyl- $\beta$ -cyclodextrin and sulfobutylether- $\beta$ -cyclodextrin.

If desired, complexation of an oxazolidinone antibiotic drug by a cyclodextrin can be increased by addition of a water-soluble polymer such as carboxymethylcellulose or a salt thereof, hydroxypropylmethylcellulose or polyvinylpyrrolidone, as described by Loftsson (1998), *Pharmazie* 53: 733-740.

The cyclodextrin is present at a concentration effective to enhance the solubility of the oxazolidinone, for example at a concentration of about 1 to about 500 mg/ml. In practice and in view of the high cost of cyclodextrins, the amount of the cyclodextrin present in a composition of the invention is preferably only slightly greater, for example no more than about 50% greater, than a minimum amount required to maintain the oxazolidinone in solution at the desired oxazolidinone concentration. The cyclodextrin is preferably present in an amount above the practical limit of solubility of the oxazolidinone.

Where the composition is intended for direct administration to an eye as formulated, the concentration of cyclodextrin in the composition is preferably from about 1 to about 500 mg/ml, more preferably about 5 to about 300 mg/ml, more preferably about 5 to about 250 mg/ml, even more preferably about 10 mg/ml to about

100 mg/ml.

The composition is preferably in the form of an aqueous solution, more preferably, one that can be presented in the form of eye drops. By means of a suitable dispenser, a desired dosage of the active agent can be metered by administration of a  
5 known number of drops into the eye, and most preferably by one drop. Suitable dispensers are illustratively disclosed in International Patent Publication No. WO 96/06581, incorporated herein by reference.

The composition of the invention preferably further comprises an ophthalmically compatible antioxidant. The antioxidant preferably enhances the  
10 antimicrobial potency of an oxazolidinone formulation of the present invention, when present. Preferred antioxidants included in the formulation include, but are not limited to: sodium bisulfite, sodium thiosulfate, acetyl cysteine, cysteine, thioglycerol, sodium sulfite, acetone sodium bisulfite, dithioerythritol, dithiothreitol, thiourea, and erythorbic acid. More preferably, the antioxidant included in the formulation is  
15 selected from the group consisting of sodium bisulfite, sodium thiosulfate, acetyl cysteine, cysteine, thioglycerol. Even more preferably, the antioxidant is sodium bisulfite.

The composition optionally further includes at least one ophthalmically acceptable salt in an amount required to bring osmolality of the composition into an  
20 ophthalmically acceptable range. In some cases, the salts can also be antioxidants, such as those cited herein, above. Salts suitable for use in adjusting osmolality include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; preferred salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and  
25 ammonium sulfate, with sodium chloride being especially preferred. Other solutes suitable for adjustment of osmolality include sugars, for example dextrose, lactose, xylitol, and mannitol and glycerine.

The composition of the invention optionally further includes at least one ophthalmically acceptable pH adjusting agent and/or buffer, including an acid such as  
30 acetic, boric, citric, lactic, phosphoric and hydrochloric acids; a base such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane, triethanolamine; and a buffer such as



citrate/dextrose, sodium bicarbonate and ammonium chloride or an amino acid. Such an acid, base and/or buffer is preferably included in an amount required to maintain pH of the composition in an ophthalmically acceptable range.

Accordingly, a particular embodiment of the invention is a composition as  
5 described hereinabove, further comprising a buffering agent and/or an agent for adjusting osmolality in amounts whereby the solution is substantially isotonic and has a physiologically acceptable pH.

A challenge for topical administration of drugs to the eye is a high rate of drug loss from the exterior of the eye. Only a small volume of fluid can be accommodated  
10 in the exterior of the eye, including the conjunctival sac, and under normal conditions lacrimal fluid fills most of the available volume. The additional volume of fluid in the form of a drug formulation that can be accepted by a human eye without washout varies from about 3  $\mu$ l to about 25  $\mu$ l, but is normally about 10  $\mu$ l. Furthermore, turnover rate of lacrimal fluid is high, typically about 16% per minute, and this can lead  
15 to rapid loss of an instilled drug by normal lacrimal drainage. Thus under normal conditions, only about 10% to about 20% of a drug dose is retained in the exterior of the eye 5 minutes after placement therein of 1-2 drops of a solution or suspension composition of the drug, and the composition is almost completely eliminated within 15 minutes. See for example Sorensen & Jensen (1979), Acta Ophthalmol.  
20 (Copenhagen) 57, 564-581. Reflex blinking and lacrimation caused by irritation from the topical administration can result in even faster drug loss.

Increasing viscosity of the instilled formulation and hence of the lacrimal fluid can reduce the rate of lacrimal drainage and thereby increase residence time of the drug in the exterior of the eye. A consequence of removal of an ophthalmic composition  
25 from a treated eye is a reduced concentration of the active agent in the lacrimal fluid and hence in the target tissue. Ointments are often used as ophthalmic formulations for this reason. However, ointments often cause discomfort by interfering with vision and free movement of the eyelids. Clear aqueous solutions and suspensions are therefore usually a preferred choice, especially for daytime administration. The ophthalmic  
30 composition of the present invention can be in the form of an ointment. However, it is preferably in the form of an aqueous solution or suspension, more preferably in the form of a clear aqueous solution.

The composition of the present invention preferably further includes at least one ophthalmically acceptable excipient ingredient that reduces the rate of removal of the composition from the eye by lacrimation, such that the composition has an effective residence time in the eye of about 2 to about 24 hours. Lacrimation is the production of tear fluid, and can remove matter from the eyes both by external wash-out and by lacrimal drainage into the nasopharyngeal cavity via the nasolacrimal ducts. A consequence of removal of an ophthalmic composition from a treated eye is a reduced concentration of the active agent in the lacrimal fluid and hence in the target tissue.

For sustained antibacterial action, the concentration in the lacrimal fluid and in the target tissue, e.g., the conjunctiva or the cornea, must remain above the  $MIC_{90}$  for the active agent in question. The  $MIC_{90}$  is the minimum inhibitory concentration for 90% of the target organisms, in this instance infective gram-positive bacteria. For example, where the active agent is linezolid, the  $MIC_{90}$  is about 4  $\mu\text{g/ml}$ . By "effective residence time" herein is meant a period of time following application of the composition to the eye during which the concentration of the active agent in the lacrimal fluid and/or in the target tissue remains above the  $MIC_{90}$  for that active agent.

The aqueous suspension or solution of the present invention is preferably viscous or mucoadhesive, or even more preferably, both viscous or mucoadhesive. In a particularly preferred embodiment, the aqueous suspension or solution/suspension of the invention contains carboxymethylcellulose, a viscosity enhancer and promoter of mucoadhesion. The concentration of carboxymethylcellulose in the aqueous suspension or solution of the present invention is preferably 0.1% to 5%, more preferably about 0.1% to about 2.5% by weight. The carboxymethylcellulose is preferably in the form of sodium carboxymethylcellulose substituted to a degree that the sodium content of the sodium carboxymethylcellulose is about 1% to about 20%.

Preferably no more than 3 drops, more preferably no more than 2 drops, and most preferably no more than 1 drop, each of about 10 to about 40  $\mu\text{l}$ , preferably about 15 to about 30  $\mu\text{l}$ , for example about 20  $\mu\text{l}$ , should contain the desired dose of the active agent for administration to an eye. Administration of a larger volume to the eye risks loss of a significant portion of the applied composition by lacrimal drainage.

Any one of a number of different excipients can be included in the composition of the present invention to increase retention of the composition in an eye. For

example, any ophthalmically compatible viscosity enhancer can be included in the composition of the present invention. An alternative class of excipients suitable for use in the compositions of the present invention are disclosed in U.S. Patent No. 4,474,751 to Haslam *et al.*, incorporated herein by reference, that describes liquid aqueous ophthalmic compositions comprising a drug, preferably a water-soluble drug, together with 10% to 50% by weight of a thermosetting polymer that forms a gel at a human body temperature. Upon placement of such a liquid composition in an eye, a gel is said to form thereby retarding loss of the drug from the eye by lacrimal drainage. Such compositions are said to be useful for ophthalmic delivery of antibacterial agents, for example vancomycin.

In a preferred embodiment, the composition is an *in situ* gellable aqueous composition, more preferably an *in situ* gellable aqueous solution. Such a composition comprises a gelling agent in a concentration effective to promote gelling upon contact with the eye or with lacrimal fluid in the exterior of the eye. Suitable gelling agents non-restrictively include thermosetting polymers such as tetra-substituted ethylene diamine block copolymers of ethylene oxide and propylene oxide (*e.g.*, poloxamine 1307); polycarbophil; and polysaccharides such as gellan, carrageenan (*e.g.*, kappa-carrageenan and iota-carrageenan), chitosan and alginate gums.

The term "*in situ* gellable" herein is to be understood as embracing not only liquids of low viscosity that form gels upon contact with the eye or with lacrimal fluid in the exterior of the eye, but also more viscous liquids such as semi-fluid and thixotropic gels that exhibit substantially increased viscosity or gel stiffness upon administration to the eye. Indeed, it can be advantageous to formulate a composition of the invention as a gel, to minimize loss of the composition immediately upon administration, as a result for example of lacrimation caused by reflex blinking. Although it is preferred that such a composition exhibit further increase in viscosity or gel stiffness upon administration, this is not absolutely required if the initial gel is sufficiently resistant to dissipation by lacrimal drainage to provide the effective residence time specified herein.

Any one of a number of *in situ* gelling excipients or systems are suitable for use in the composition of the present invention, including but not limited to the following.

U.S. Patent No. 4,861,760 to Mazuel & Friteyre, incorporated herein by

reference, discloses a liquid *in situ* gelling composition said to be suitable for ophthalmic use. The composition contains in aqueous solution a polysaccharide that undergoes liquid-gel phase transition in response to ionic strength of tear fluid. A suitable polysaccharide is gellan gum, which can be used in a concentration of 0.1% to 2% by weight of the composition. Such a composition is said to be useful for ophthalmic delivery of antibacterial agents, for example vancomycin.

In a particularly preferred embodiment, the composition is an *in situ* gellable aqueous solution, suspension or solution/suspension having excipients substantially as disclosed in above-cited U.S. Patent No. 4,861,760, comprising about 0.1% to about 2% by weight of a polysaccharide that gels when it contacts an aqueous medium having the ionic strength of lacrimal fluid. A preferred such polysaccharide is gellan gum, more preferably a low acetyl clarified grade of gellan gum such as that sold under the trademark Gelrite®. Suitable partially deacylated gellan gums are disclosed in U.S. Patent No. 5,190,927 to Chang & Kobzeff, incorporated herein by reference.

Preferably the drug is in solution in the composition.

U.S. Patent No. 5,192,535 to Davis *et al.*, incorporated herein by reference, discloses liquid compositions said to be suitable for use as eye drops, utilizing a different *in situ* gelling mechanism. These compositions contain a lightly cross-linked carboxyl-containing polymer such as polycarbophil and have a pH of about 3.0 to about 6.5. Upon placement of such a composition in an eye, contact with lacrimal fluid having a pH of about 7.2 to about 7.4 is said to result in gelling and consequent increase of residence time in the eye, permitting sustained release of a drug contained in the composition. Drugs for which such a composition is said to be useful include antibiotics, for example vancomycin.

In a particularly preferred embodiment, the composition is an *in situ* gellable aqueous solution having excipients substantially as disclosed in above-cited U.S. Patent No. 5,192,535, comprising about 0.1% to about 6.5%, preferably about 0.5% to about 4.5%, by weight, based on the total weight of the composition, of one or more lightly cross-linked carboxyl-containing polymers, and preferably having the oxazolidinone drug in solution. Such an aqueous composition has a pH of about 3 to about 6.5, preferably about 4 to about 6. A preferred polymer in this embodiment is polycarbophil, which causes the composition to gel upon contact with lacrimal fluid in

the eye, which has a typical pH of about 7.2 to about 7.4. This formation of a gel enables the composition to remain in the eye for a prolonged period without loss by lacrimal drainage.

U.S. Patent No. 5,212,162 to Missel *et al.*, incorporated herein by reference, discloses further liquid *in situ* gelling compositions said to be suitable for ophthalmic use. The compositions contain a drug together with a finely-divided (conveniently about 1 to about 25  $\mu\text{m}$  particle size) carrier that binds with the drug, and a gelling polysaccharide, preferably a carrageenan, especially a carrageenan having not more than 1.0 sulfate moiety per disaccharide unit, e.g., eucheuma carrageenan, kappa-carrageenan or furcellaran. Such compositions are said to be useful for ophthalmic delivery of anti-infective agents, for example ciprofloxacin.

U.S. Patent No. 5,403,841 to Lang *et al.*, incorporated herein by reference, discloses further liquid *in situ* gelling compositions said to be suitable for ophthalmic use. These compositions contain a carrageenan having not more than 1.0 sulfate moiety per disaccharide unit that is capable of gelling in 0.5% to 1.0% aqueous sodium chloride solution. Such compositions are said to be useful for ophthalmic delivery of anti-infective agents, for example ciprofloxacin.

U.S. Patent No. 5,587,175 to Viegas *et al.*, incorporated herein by reference, discloses further liquid *in situ* gelling compositions said to be suitable for ophthalmic use. These compositions contain an ionic polysaccharide, for example gellan gum, alginate gum or chitosan, and a film-forming agent, for example hydroxypropyl methylcellulose, carboxymethylcellulose, sodium chondroitin sulfate, sodium hyaluronate, polyvinylpyrrolidone, *etc.* The compositions are pH buffered to match pH of tear fluid. Gelling is said to occur upon contact with calcium ions. Such compositions are said to be useful for ophthalmic delivery of antibacterial agents, for example vancomycin.

U.S. Patent No. 5,876,744 to Della Valle *et al.*, incorporated herein by reference, discloses bioadhesive and mucoadhesive compositions, including some said to be useful as ophthalmic compositions, comprising mixtures of synthetic polymers such as polycarbophil and polyvinyl alcohol and biopolymers such as alginic acid, hyaluronic acid and dermatan sulfate. Such compositions are said to be capable of increasing contact time with a treated eye of specific drugs.

European Patent No. 0 424 043, incorporated herein by reference, discloses a liquid ophthalmic composition comprising a sulfated polysaccharide or derivative thereof that undergoes a liquid-gel transition on interaction with proteins of the lacrimal fluid in the eye. Such sulfated polysaccharides are said to include kappa-  
5 carrageenan, iota-carrageenan and mixtures thereof. The composition is said to be useful for ophthalmic delivery of antibacterial agents.

In another particularly preferred embodiment, the composition is an *in situ* gellable aqueous solution containing xanthan gum, substantially as disclosed in U.S. Patent No. 6,174,524.

10 In another particular embodiment the composition is an *in situ* gellable aqueous solution excipients substantially as disclosed in above-cited European Patent No. 0 424 043, comprising about 0.1% to about 5% of a carrageenan gum. Carrageenans are sulfated polysaccharides; in this embodiment a carrageenan having no more than 2 sulfate groups per repeating disaccharide unit is preferred, including kappa-  
15 carrageenan, having 18-25% ester sulfate by weight, iota-carrageenan, having 25-34% ester sulfate by weight, and mixtures thereof. As indicated above, and contrary to the teaching of above-cited European Patent No. 0 424 043, where a preservative is to be included, it is preferred according to the present invention to select a preservative that does not precipitate in the composition.

20 In another particular embodiment the composition comprises an ophthalmically acceptable mucoadhesive polymer, selected for example from hydroxypropylmethylcellulose, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, polyethylene oxide, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

25 Optionally, an ophthalmically acceptable xanthine derivative such as caffeine, theobromine or theophylline can be included in the composition, substantially as disclosed in U.S. Patent No. 4,559,343 to Han & Roehrs, incorporated herein by reference. Inclusion of the xanthine derivative can reduce ocular discomfort associated with administration of the composition.

30 Optionally, one or more ophthalmically acceptable surfactants, preferably nonionic surfactants, can be included in the composition to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid

glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

Optionally, one or more antioxidants can be included in the composition to enhance chemical stability where required. Suitable antioxidants include ascorbic acid  
5 and sodium metabisulfite.

One or more ophthalmic lubricating agents can optionally be included in the composition to promote lacrimation or as a "dry eye" medication. Such agents include polyvinyl alcohol, methylcellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, etc. It will be understood that promotion of lacrimation is  
10 beneficial in the present invention only where lacrimation is naturally deficient, to restore a normal degree of secretion of lacrimal fluid. Where excessive lacrimation occurs, residence time of the composition in the eye can be reduced.

A composition of this particular embodiment can optionally further comprise glycerin in an amount of about 0.5% to about 5%, more preferably about 1% to about  
15 2.5%, for example about 1.5% to about 2%, by weight. Glycerin can be useful to increase viscosity of the composition and for adjustment of osmolality. Independently of the presence of glycerin, a composition of this particular embodiment can optionally further comprise a cyclodextrin, preferably hydroxypropyl- $\beta$ -cyclodextrin, in an amount of about 1 mg/ml to about 500 mg/ml by weight. Such a cyclodextrin can be  
20 useful as a solubilizing agent as described above.

In another embodiment, the composition is either used in co-therapy, co-administration, or coformulated with at least one drug other than an antibacterial agent. In a preferred embodiment, the composition of the present invention further comprises a therapeutically and/or prophylactically effective amount of the at least one  
25 drug other than an antibacterial agent. The drug other than an antibacterial agent can cooperate with the oxazolidinone antibacterial drug(s) in the composition in treating and/or preventing an infective disease of the eye, or can be used to treat a related or unrelated condition simultaneously affecting the eye.

Any drug having utility as a topical ophthalmic application can be used in co-  
30 therapy, co-administration or coformulation with a composition of the invention as described immediately above. Such drugs include without limitation demulcents; antimycotics, antivirals and other anti-infectives; acetylcholine blocking agents;

- adrenergic agonists, beta-adrenergic blocking agents and other antiglaucoma agents; antihypertensives; antihistamines; anticataract agents; and topical and regional anesthetics. Illustrative specific drugs include acebutolol, aceclidine, acetylsalicylic acid (aspirin), N<sup>d</sup> acetylsulfisoxazole, alclofenac, alprenolol, amfenac, amiloride,
- 5 aminocaproic acid, *p*-aminoclonidine, aminozolamide, anisindione, apafant, atenolol, bacitracin, benoxaprofen, benoxinate, benzofenac, bepafant, betamethasone, betaxolol, bethanechol, bimatoprost, brimonidine, bromfenac, bromhexine, bucloxic acid, bupivacaine, butibufen, carbachol, carprofen, celecoxib, cephalexin, chloramphenicol, chlordiazepoxide, chlorprocaine, chlorpropamide, chlortetracycline, cicloprofen,
- 10 cinmetacin, ciprofloxacin, clidanac, clindamycin, clonidine, clonixin, clopirac, cocaine, cromolyn, cyclopentolate, cyproheptadine, demecarium, dexamethasone, dibucaine, diclofenac, diflusal, dipivefrin, dorzolamide, enoxacin, epinephrine, erythromycin, eserine, estradiol, ethacrynic acid, etidocaine, etodolac, fenbufen, fenclofenac, fenclorac, fenoprofen, fentiazac, flufenamic acid, flufenisal, flunoxaprofen,
- 15 fluoroquinolone, fluorometholone, flurbiprofen and esters thereof, fluticasone propionate, furaprofen, furobufen, furofenac, furosemide, gancyclovir, gentamicin, gramicidin, hexylcaine, homatropine, hydrocortisone, ibufenac, ibuprofen and esters thereof, idoxuridine, indomethacin, indoprofen, interferons, isobutylmethylxanthine, isofluorophate, isoproterenol, isoxepac, ketoprofen, ketorolac, labetolol, lactorolac,
- 20 latanoprost, levo-bunolol, lidocaine, lonazolac, loteprednol, meclofenamate, medrysone, mefenamic acid, mepivacaine, metaproterenol, methanamine, methylprednisolone, metiazinic, metoprolol, metronidazole, minopafant, miroprofen, MK-663, modipafant, nabumetone, nadolol, namoxyrate, naphazoline, naproxen and esters thereof, neomycin, nepafenac, nitroglycerin, norepinephrine, norfloxacin,
- 25 nupafant, ofloxacin, olopatadine, oxaprozin, oxepinac, oxyphenbutazone, oxyprenolol, oxytetracycline, parecoxib, penicillins, perfloxacin, phenacetin, phenazopyridine, pheniramine, phenylbutazone, phenylephrine, phenylpropanolamine, phospholine, pilocarpine, pindolol, pirazolac, piroxicam, pirprofen, polymyxin, polymyxin B, prednisolone, prilocaine, probenecid, procaine, proparacaine, protizinic acid,
- 30 rimexolone, rofecoxib, salbutamol, scopolamine, sotalol, sulfacetamide, sulfamic acid, sulindac, suprofen, tenoxicam, terbutaline, tetracaine, tetracycline, theophyllamine, timolol, tobramycin, tolmetin, travoprost, triamcinolone, trimethoprim,



trospoctomycin, valdecoxib, vancomycin, vidarabine, vitamin A, warfarin, zomepirac and pharmaceutically acceptable salts thereof.

Compositions of the present invention can be prepared by processes known in the art, including by simple admixture, with agitation as appropriate, of the ingredients.

- 5 Preferably, an aqueous solution of the cyclodextrin compound is first prepared, and the oxazolidinone in finely divided solid particulate form is added to that solution with agitation until it is fully dissolved. Where it is desired to prepare a buffered isotonic solution buffering agents and agents for adjustment of osmolality can be added at any stage but are preferably present in solution with the cyclodextrin compound before
- 10 addition of the oxazolidinone. Similarly, where it is desired to include any of the other additional alternative components cited above in the composition they can be added at any stage, but, are preferably present in the solution with the cyclodextrin compound before addition of the oxazolidinone. Processes for preparing an ophthalmic composition of the invention are preferably conducted so as to provide a sterile
- 15 product.

- Aqueous suspension compositions of the invention can be packaged in single-dose non-reclosable containers. Such containers can maintain the composition in a sterile condition and thereby eliminate need for preservatives such as mercury-containing preservatives, which can sometimes cause irritation and sensitization of the
- 20 eye. Alternatively, multiple-dose reclosable containers can be used, in which case it is preferred to include a preservative in the composition.

In a method of the invention for treating or preventing infective disease, an ophthalmic composition as described above in a therapeutically or prophylactically effective dose is administered to at least one eye of a subject in need thereof.

- 25 In a method of the invention, a composition as herein described is administered topically in an antibacterially effective amount to an eye that is infected by one or more bacterial organisms. The eye is of a warm-blooded, preferably a mammalian subject. Suitable mammalian subjects include domestic mammals, farm and exotic mammals, and humans. The method can be useful, for example, in treatment of eye infections of
- 30 dogs, cats, horses, cattle, sheep and pigs, but is more particularly useful where the subject is human.

As indicated above, a method of the invention is particularly useful where the

infective disease arises through infection by one or more gram-positive bacteria.

Where broader-spectrum antibacterial activity is required, a second antimicrobial drug can be administered in co-therapy, including for example, coformulation, with the present composition. When the first antibiotic drug is effective against gram-positive  
5 bacteria, the second antimicrobial drug is selected to be effective against target gram-negative bacteria. Such co-therapy and coformulation are embodiments of the present invention.

The second antimicrobial drug can illustratively be selected from aminoglycosides, cephalosporins, diaminopyridines, fluoroquinolones, sulfonamides and  
10 tetracyclines. Among particular antimicrobial drugs of these and other classes, each of the following may illustratively be useful as the second antimicrobial drug according to an embodiment of the present invention: amikacin, cefixime, cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, chloramphenicol, ciprofloxacin, clindamycin, colistin, doxycycline, doxycycline, gentamicin, mafenide, methacycline,  
15 minocycline, neomycin, norfloxacin, ofloxacin, oxytetracycline, polymyxin B, pyrimethamine, silver sulfadiazine, sulfacetamide, sulfisoxazole, tetracycline, tobramycin and trimethoprim.

The composition of the present invention preferably does not contain any drugs such as an anti-inflammatory agent (ie. a COX-2 inhibitor) likely to interfere with  
20 solubilization of any antibiotic drug or antibiotic activity of any antibiotic drug contained therein.

In a method of the invention, a composition as herein described as comprising an antibiotic effective against gram-positive bacteria is administered topically in an antibacterially effective amount to an eye that is infected by one or more gram-positive  
25 bacterial organisms.

In a preferred method, the gram-positive bacterial organism(s) are species of *Staphylococcus* (e.g., *Staphylococcus aureus*, *Staphylococcus epidermidis*), *Streptococcus* (e.g., *Streptococcus viridans*, *Streptococcus pneumoniae*), *Enterococcus*, *Bacillus*, *Corynebacterium*, *Propionibacterium*, *Chlamydia*,  
30 *Moraxella*, *Haemophilus* and *Neisseria*. In an especially preferred method, the gram-positive bacterial organism(s) are of strain(s) that have developed significant levels of resistance to antibacterial agents other than the oxazolidinone antibacterial agent(s),

e.g., linezolid, in the composition being administered.

Treatment of bacterial conjunctivitis by the method of the invention is appropriate, for example, where infection with one or more of the following species is present: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Enterococcus faecalis*, *Corynebacterium* sp., *Propionibacterium* sp., *Moraxella catarrhalis* and *Haemophilus influenzae*.

Treatment of bacterial blepharitis by the method of the invention is appropriate, for example, where infection with one or more of the following species is present:

10 *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pneumoniae*.

Treatment of bacterial keratitis by the method of the invention is appropriate, for example, where infection with one or more of the following species is present: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae* and *Streptococcus viridans*.

15 Prophylaxis of bacterial infection of the eye prior to ocular surgery by the method of the invention is appropriate, for example, where a risk exists of infection with one or more of the following species: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Corynebacterium* sp. and *Propionibacterium* sp.

In another embodiment, the method is used to administer a composition comprising an antibiotic effective against gram-negative bacteria. An appropriate dosage, frequency and duration of administration, i.e., treatment regimen, to be used in any particular situation will be readily determined by one of skill in the art without undue experimentation, and will depend, among other factors, on the particular antibiotic drug(s) present in the composition, on the particular ophthalmic infective condition being treated, on the age, weight and general physical condition of the subject, and on other medication being administered to the subject. It is preferred that response of the ophthalmic infective condition to treatment according to the present method be monitored and the treatment regimen be adjusted if necessary in light of such monitoring.

30 Frequency of administration is typically such that the dosing interval, i.e., the period of time between one dose and the next, during waking hours is about 2 to about 12 hours, more typically about 3 to about 8 hours, for example about 4 to about

6 hours. It will be understood by those of skill in the art that an appropriate dosing interval is dependent to some degree on the length of time for which the selected composition is capable of maintaining a concentration of the oxazolidinone antibiotic in the lacrimal fluid and/or in the target tissue (e.g., the conjunctiva) above the MIC<sub>90</sub>.

- 5 Ideally the concentration remains above the MIC<sub>90</sub> for at least 100% of the dosing interval. Where this is not achievable it is desired that the concentration should remain above the MIC<sub>90</sub> for at least about 60% of the dosing interval, in a worst case at least about 40% of the dosing interval.

- 10 The following examples are illustrative of the process and products of the present invention. They are not to be construed as limiting. All experiments were or are done at room temperature and pressure, unless otherwise indicated.

#### EXAMPLES

The following Examples illustrate aspects of the present invention but are not to be construed as limitations.

15 Example 1 - Solubility of Linezolid in Sulfobutylether- $\beta$ -Cyclodextrin

A study was conducted to examine solubility of linezolid in an aqueous system containing sulfobutylether- $\beta$ -cyclodextrin (SB- $\beta$ -CD).

- 20 Aqueous solutions of SB- $\beta$ -CD at concentrations of 10, 50, 100, 150, 250 and 500 mg/ml were prepared. Excess linezolid was added to each solution. The solutions were stirred for 24 h at 25°C and were then filtered using 0.2  $\mu$ m Gelman Acrodisc filter units and assayed for linezolid by HPLC.

Saturation solubility of linezolid in pure water at pH 7 was determined separately to be  $2.9 \pm 0.1$  mg/ml. Saturation solubility of linezolid in aqueous SB- $\beta$ -CD solutions was determined as shown in Table 1.

25 **Table 1. Saturation solubility of linezolid in SB- $\beta$ -CD solutions**

SB- $\beta$ -CD concentration (mg/ml)	Solubility of linezolid (mg/ml)
10	4.3
50	9.5
100	15.9
150	22.1
250	33.4
500	59.9

### Example 2 - Solubility of Three Oxazolidinones in Hydroxypropyl- $\beta$ -Cyclodextrin

A study was conducted to examine solubility of three oxazolidinone compounds, herein denoted Compound 1, Compound 2 and Compound 3, in an aqueous system containing hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD).

5       Compound 1 is (S)-N-[[3-[3-fluoro-4-(4-(hydroxyacetyl)-1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

Compound 2 is (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (linezolid).

10       Compound 3 is (S)-N-[[3-[3-fluoro-4-(1,1-dioxothiomorpholin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

Aqueous solutions of HP- $\beta$ -CD at concentrations of 0, 60, 100, 200, 300 and 400 mg/ml were prepared. Compound 1, 2 or 3 in excess amount was added to each solution. The solutions were stirred for 48 h at 37°C and were then filtered and assayed by HPLC to provide a measure of saturation solubility of Compounds 1, 2 and  
15       3 in each HP- $\beta$ -CD solution.

The saturation solubilities are shown in graphical form in Fig. 1. Saturation solubility of each oxazolidinone compound was found to be linearly related to HP- $\beta$ -CD concentration.

### Example 3 - Tests for Preservative Effectiveness

20       Several ophthalmic formulations were prepared, as described in the Examples, below, and tested for preservative effectiveness in accordance with United States Pharmacopean ("USP XXIV") and European Pharmacopean ("EP") criteria, as described herein, below. These are standard tests and conventionally utilized to determine the preservative efficacy of any given preservative or preserved  
25       composition. Microorganisms specified in the compendia as well environmental isolates are used for examining the ability of the formulations to meet the criteria.

The compendia specify log reductions criteria as follows:

USP XXIV	EP
30       Category 1A aqueous based Injectables, including emulsions, otics Sterile nasal products and ophthalmics	Aqueous formulated parenteral and ophthalmic preparations

Test Criteria	7d	14d	28d	6h	24h	7d	14d	28d
Bacteria	1	3	NI	A 2	3	--	--	--
				B --	1	3	--	--
Molds & Yeasts	NI	NI	NI	A --	--	2	--	NI
				B --	--	--	1	NI

It is understood that the above criteria can be ranked in increasing order of strictness as: USP < EP B < EP A. The term "NI", as used herein, refers to no increase in growth observed.

The target is thus to meet EP A and, failing that, to meet EP B.

#### Example 4 Preparation of Linezolid Ophthalmic Formulations

Three types of ophthalmic formulations containing linezolid as the active agent were prepared as described in Tables 1-3, below. Table 1 describes formulations prepared with only solubilized drug. Formulations described in Table 2 contained a neutral polymeric system to enhance residence time of the formulation in the eye. Formulations in Table 3 included an anionic polymer system to enhance the residence time of the formulation in the eye. Either of two quaternary ammonium preservatives was used in all but one of the compounds described in Tables 1 through 3, benzalkonium chloride ("BAC") or cetyl pyridinium chloride ("CPC"). Sodium bisulfite/metabisulfite was included in some formulations, but not in others.

It is generally known that polymers, and especially charged polymers, are often incompatible with many common preservatives. Thus, in addition to the difficulty presented in identifying preservatives compatible with cyclodextrins and oxazolidinones, the formulations in Table 3 present an extra level of difficulty in identifying formulations that can provide effective antimicrobial preservation.

Table 1: Solution formulations with no thickener

ID	Active ingredient (%)	Cyclodextrin level (%)	Polymer system	EDTA (%)	BAC (%)	CPC (%)	Na Bisulfite (%)	Other
1	5	25	-	0.1	-	0.01	-	Adjusted to pH 5.0
2	5	25	-	0.1	-	0.05	-	Adjusted to pH 5.0

Table 2: Formulations containing neutral polymers

ID	Active ingredient (%)	Cyclodextrin level (%)	Polymer system	EDTA (%)	BAC (%)	CPC (%)	Na Bisulfite (%)	Other
3	1	5	HPGuar/Agarose	0.1	0.02	-	-	Adjusted to pH 5.2
4	1	5	HPGuar/Agarose	0.1	-	0.02	-	Adjusted to pH 5.5
5	5	25	HPGuar/Agarose	0.1	-	0.02	-	0.05M Citrate buffer, pH 5.0
6	5	25	HPGuar/Agarose	0.1	-	0.05	-	0.05M Citrate buffer, pH 5.0
7	5	25	HPGuar/Agarose	0.1	-	0.05	0.1	0.05M Citrate buffer, pH 5.0

Table 3: Formulations containing anionic polymers

ID	Active ingredient (%)	Cyclodextrin level (%)	Polymer system	EDTA (%)	BAC (%)	CPC (%)	Na Bisulfite (%)	Other
8	1	5	Carra-genans	0.1	-	-	0.2	Adjusted to pH 6.0
9	2	10	NaCMC	0.1	0.02	-	-	Adjusted to pH 6.0
10	4	20	NaCMC	0.1	0.02	-	-	Adjusted to pH 6.0
11	2	10	NaCMC	0.1	-	0.053	-	0.05M Citrate buffer, pH 4.8
12	4	20	NaCMC	0.1	-	0.042	-	0.05M Citrate buffer, pH 4.8
13	5	25	NaCMC	0.1	-	0.05	0.02	0.05M Citrate buffer, pH 4.9
14	5	25	NaCMC	0.1	-	0.05	0.05	0.05M Citrate buffer, pH 4.8

ID	Active ingredient (%)	Cyclodextrin level (%)	Polymer system	EDTA (%)	BAC (%)	CPC (%)	Na Bisulfite (%)	Other
15	5	25	NaCMC	0.1	-	0.05	0.08	0.05M Citrate buffer, pH 5.0
16	5	25	NaCMC	0.1	-	0.05	0.1	0.05M Citrate buffer, pH 5.0

All concentrations in Tables 1 through 3, above are in (%) w/w. NaCMC in Table 3 was used at 1% level. In Table 2, HPGuar was at 0.5%, and was Agarose at 0.13%. BAC: Benzalkonium chloride; CPC: CetylPyridinium Chloride; NaBisulfite:

- 5 Sodium Bisulfite; NaCMC: Sodium Carboxymethyl Cellulose; HPGuar: HydroxyPropyl Guar.

Example 5 - Results of Testing Linezolid Ophthalmic Solutions

- Formulations prepared as described in Example 4, above, were tested according to the procedure set forth in Example 3, above. Specifically, all the
- 10 formulations were first tested on an abbreviated test plan comprising a reduced set of organisms. The full test plan was implemented only if the organisms in the abbreviated test all passed EP B criteria at 24 hours. It was found that the abbreviated testing was very predictive of the full testing results.

The results are summarized in Tables 4, 5, 6, below.

- 15 Table 4 shows that a certain level of CPC is needed before preservative effectiveness is achieved in a cyclodextrin containing system. ID# 1, containing only 0.01% CPC failed EP A and B testing. In contrast, ID# 2, containing 0.05% CPC passed EP A for all but one organism tested, and passed EP B for that organism.

- 20 Table 4: Results of AET testing on solution formulations from Table 1.

ID	BAC (%)	CPC (%)	Na Bisulfite (%)	Organism	Log reduction achieved in				Comments
					6 hrs	24 hrs	7 days	14 days	
1	-	0.01	-	<i>Staph. aureus</i>	-0.3	-0.1			Discontinued testing. Fails EP A and B
				<i>E. Coli</i>	0.2	0.2			
				<i>Staph. Sp.</i>	0.5	0.1			



2	-	0.05	-	<i>Staph. aureus</i>	0.4	GT3.9	GT3.9	GT3.9	Test expanded with other organisms, which all pass EPA except <i>Staph. aur</i> at 6 hrs. All pass EP B
				<i>E. Coli</i>	2.4	3.7	GT6.8	GT6.8	
				<i>Staph. Sp.</i>	1.9	GT3.7	GT3.7	GT3.7	

Table 5 shows that while BAC at 0.02% was not effective (ID# 3), CPC at 0.02% was surprisingly effective passing EP A (ID#'s 4 and 5) in formulations containing 5% Cyclodextrin. However, increasing the cyclodextrin level to 25% required higher levels of CPC (up to 0.05%; compare ID# 4 to #5). Addition of NaBisulfite surprisingly improves the preservative effectiveness (compare ID #6 to #7) allowing this formulation to pass EP B.

Table 5: Results of AET testing on formulations containing neutral polymers (HPGuar/Agarose) from Table 2

ID	BAC (%)	CPC (%)	Na Bisulfite (%)	Organism	Log reduction achieved in				Comments
					6 hrs	24 hrs	7 days	14 days	
3	0.02	-	-	<i>Staph. aureus</i>	0.1	1.1			Discontinued testing. <i>E. Coli</i> fails EP B.
				<i>E. Coli</i>	-0.1	-0.2			
				<i>Staph. Sp.</i>	2.5	GT4.6			
4	-	0.02	-	<i>Staph. aureus</i>	GT4.6	GT4.6	GT4.6	GT4.6	Test expanded with other organisms, which all pass EPA
				<i>E. Coli</i>	3.1	GT6.9	GT6.9	GT6.9	
				<i>Staph. Sp.</i>	GT4.6	GT4.6	GT4.6	GT4.6	
5	-	0.02	-	<i>Staph. aureus</i>	0.6	0.8			Discontinued testing. <i>Staph. aur.</i> fails EP B.
				<i>E. Coli</i>	0.6	1.6			
				<i>Staph. Sp.</i>	1.8	2.1			
6	-	0.05	-	<i>Staph. aureus</i>	0.4	0.3			Discontinued testing. <i>Staph. aur.</i> and <i>Staph. Sp.</i> fail EP B.
				<i>E. Coli</i>	2.1	2.5			
				<i>Staph. Sp.</i>	0.5	0.8			
7	-	0.05	0.1	<i>Staph. aureus</i>	0.4	GT3.8			All organisms pass EP A
				<i>E. Coli</i>	1.8	4			

				<i>Staph. Sp.</i>	2.3	GT3.7			except <i>Staph Aur</i> at 6 hrs. All Pass EP B
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Table 6, below, shows that 0.02% BAC was found not to be an effective preservative in formulations containing 20 or even 10% cyclodextrin (ID# 9, ID#10). An improved efficacy was seen with CPC at 0.05% level (ID# 11, ID# 12). Addition of small amounts of NaBisulfite greatly improved the preservative efficacy (ID#'s 13-16). However, NaBisulfite by itself was found not to be an effective preservative. See, for example, the results for ID# 8 in Table 6, showing that a linezolid solution with cyclodextrin and 0.2% NaBisulfite and no CPC or BAC failed the EP B test with *E. coli* after only 24 hours.

10

Table 6: Results of AET testing on formulations containing anionic polymer (NaCMC) from Table 3

ID	BAC (%)	CPC (%)	Na Bisulfite (%)	Organism	Log Reduction achieved in				Comments
					6 hrs	24 hrs	7 days	14 days	
8	-	-	0.2	<i>Psued. Aur</i>	0.8	1.6			Discontinued testing. Fails EP B <i>E. Coli</i> at 24 hrs
				<i>E. Coli</i>	0.5	0.3			
				<i>Psued. Sp.</i>	2.1	3.6			
9	0.02	-	-	<i>Staph. aureus</i>	0.2	0.4			Discontinued testing. All fail EP B except <i>Staph. Sp.</i> at 24 hrs.
				<i>E. Coli</i>	0.1	0.1			
				<i>Staph. Sp.</i>	0.3	1.3			
10	0.02	-	-	<i>Staph. aureus</i>	0.2	0.2			Discontinued testing. All fail EP B except <i>Staph. Sp.</i> at 24 hrs.
				<i>E. Coli</i>	0.2	0.3			
				<i>Staph. Sp.</i>	0.2	1.0			
11	-	0.05 3	-	<i>Staph. aureus</i>	0.0	1.6	GT3.2		Test expanded with other organisms, which all pass EP B but not EP A at 6 hrs.
				<i>E. Coli</i>	1.8	2.7	GT5.5		
				<i>Staph. Sp.</i>	0.3	2.3			
12	-	0.04 2	-	<i>Staph. aureus</i>	0.0	0.3	GT3.2		<i>Staph. Aur</i> fails EP B

ID	BAC (%)	CPC (%)	Na Bisulfite (%)	Organism	Log Reduction achieved in				Comments
					6 hrs	24 hrs	7 days	14 days	
				<i>E. Coli</i>	1.9	2.7	GT5.5		at 24 hrs. Test expanded with other organisms, which all pass EP B but not EP A at 6 hrs.
				<i>Staph. Sp.</i>	0.2	2.0			
13	-	0.05	0.02	<i>Staph. aureus</i>	0.2	2.8			All organisms pass EP A except <i>Staph Aur</i> and <i>Staph. Sp.</i> at 6 hrs. All Pass EP B
				<i>E. Coli</i>	1.8	3.4			
				<i>Staph. Sp.</i>	0.9	GT3.0			
14	-	0.05	0.05	<i>Staph. aureus</i>	0.4	GT3.3			All organisms pass EP A except <i>Staph Aur</i> at 6 hrs. All Pass EP B
				<i>E. Coli</i>	1.1	4.1			
				<i>Staph. Sp.</i>	2.2	GT2.2			
15	-	0.05	0.08	<i>Staph. aureus</i>	0.5	GT3.3			All organisms pass EP A except <i>Staph Aur</i> and <i>E. Coli</i> at 6 hrs. All Pass EP B
				<i>E. Coli</i>	0.6	3.8			
				<i>Staph. Sp.</i>	GT3.0	GT3.0			
16	-	0.05	0.1	<i>Staph. aureus</i>	0.3	2.9			All organisms pass EP A except <i>Staph Aur</i> at 6 hrs. All Pass EP B
				<i>E. Coli</i>	1.2	3.8			
				<i>Staph. Sp.</i>	2.7	3.7			

#### Example 6 - Preparation and Testing of Additional Linezolid Formulations

Additional sets of samples are prepared as described in Example 4, and tested as described in Example 3, above, using in place of sodium bisulfite, at least one antioxidant selected from: Sodium thiosulfate, acetyl cysteine, cysteine, thioglycerol, sodium sulfite, acetone sodium bisulfite, dithioerythritol, dithiothreitol, thiourea, and

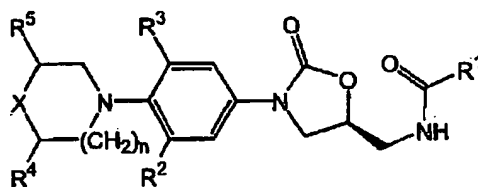
erythorbic acid. In the case of sodium thiosulfate, acetyl cysteine, and cysteine, the concentration of antioxidant in at least one sample of the formulation tested is 0.25%. In the case of thioglycerol, the concentration of antioxidant in at least one sample of the formulation tested is 0.5%.

5

## CLAIMS

What is claimed is:

1. A pharmaceutical composition suitable for topical administration to an eye, comprising:
  - 5 (a) an antibiotic drug in an antibiotic concentration effective for treatment and/or prophylaxis of a gram-positive bacterial infection of at least one tissue of the eye;
  - (b) a pharmaceutically acceptable cyclodextrin compound in a cyclodextrin concentration sufficient to maintain the drug in solution; and
  - 10 (c) cetyl pyridinium chloride.
2. The composition of claim 1, wherein the antibiotic drug is an oxazolidinone antibiotic drug and the bacterial infection is a gram-positive bacterial infection.
3. The composition of claim 2 wherein the oxazolidinone antibiotic drug is a compound of formula (I)



(I)

wherein:

R<sup>1</sup> is selected from (a) H, (b) C<sub>1-8</sub> alkyl optionally substituted with at least one F, Cl, OH, C<sub>1-8</sub> alkoxy, and C<sub>1-8</sub> acyloxy or C<sub>1-8</sub> benzyloxy, including a C<sub>3-6</sub> cycloalkyl group, (c) amino, (d) mono- and di(C<sub>1-8</sub> alkyl)amino and (e) C<sub>1-8</sub> alkoxy groups;

R<sup>2</sup> and R<sup>3</sup> are each independently selected from H, F and Cl;

R<sup>4</sup> is H or CH<sub>3</sub>;

R<sup>5</sup> is selected from H, CH<sub>3</sub>, CN, CO<sub>2</sub>R<sup>1</sup> and (CH<sub>2</sub>)<sub>m</sub>R<sup>6</sup>, where R<sup>1</sup> is as defined above, R<sup>6</sup> is selected from H, OH, OR<sup>1</sup>, OCOR<sup>1</sup>, NHCOR<sup>1</sup>, amino, mono- and di(C<sub>1-8</sub> alkyl)amino groups, and m is 1 or 2;

n is 0, 1 or 2; and

X is O, S, SO, SO<sub>2</sub>, SNR<sup>7</sup> or S(O)NR<sup>7</sup> where R<sup>7</sup> is selected from H, C<sub>1-4</sub> alkyl (optionally substituted with one or more F, Cl, OH, C<sub>1-8</sub> alkoxy, amino, C<sub>1-8</sub> mono- or di(C<sub>1-8</sub> alkyl)amino groups), and p-toluenesulfonyl groups;

5 or a pharmaceutically acceptable salt thereof.

4. The composition of claim 3 wherein, is CH<sub>3</sub>; R<sup>2</sup> and R<sup>3</sup> are independently selected from H and F but at least one of R<sup>2</sup> and R<sup>3</sup> is F; R<sup>4</sup> and R<sup>5</sup> are each H; n is 1; and X is selected from O, S and SO<sub>2</sub>.

5. The composition of claim 2 wherein the oxazolidinone antibiotic drug is  
10 selected from the group consisting of: linezolid, eperezolid, N-((5S)-3-(3-fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide, (S)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide, (S)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride and N-[[[(5S)-3-[4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.  
15

6. The composition of claim 2 wherein the oxazolidinone antibiotic drug is linezolid.

7. The composition of claim 2, wherein the oxazolidinone antibiotic drug is  
20 present at a concentration is about 0.1 mg/ml to about 100 mg/ml.

8. The composition of claim 1 wherein the cyclodextrin compound is selected from the group consisting of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, an alkylcyclodextrin, a hydroxyalkylcyclodextrin, a carboxyalkylcyclodextrin, and sulfoalkylether cyclodextrin.

25 9. The composition of claim 1 wherein the cyclodextrin compound is selected from the group consisting of hydroxypropyl-β-cyclodextrin and

sulfobutylether- $\beta$ -cyclodextrin.

10. The composition of claim 1 wherein the cyclodextrin compound is present at a concentration of about 1 to about 500 mg/ml.
11. The composition of claim 1, wherein the cetyl pyridinium chloride is present at  
5 a concentration of about 0.001 to about 10 mg/ml.
12. The composition of claim 1, further comprising an antioxidant.
13. The composition of claim 12, wherein the antioxidant is selected from the group consisting of sodium thiosulfate, acetyl cysteine, and thioglycerol.
14. The composition of claim 12, wherein the antioxidant is selected from the  
10 group consisting of sodium sulfite, acetone sodium bisulfite, dithioerythritol, dithiothreitol, thiourea, and erythorbic acid.
15. The composition of claim 12, wherein the antioxidant is sodium bisulfite.
16. The composition of claim 1, further comprising at least one ophthalmically acceptable excipient that reduces a rate of removal of the composition from  
15 the eye by lacrimation, such that the composition has an effective residence time in the eye of about 2 to about 24 hours.
17. The composition of claim 1, further comprising an *in situ* gellable material in a form selected from a solution, a suspension and a solution/suspension, wherein the *in situ* gellable material has an ophthalmically compatible pH and  
20 osmolality.
18. The composition of claim 1, further comprising a buffering agent and/or an agent for adjusting osmolality in amounts whereby the solution is substantially isotonic and has an ophthalmically acceptable pH.
19. A method of treating an eye infection in a subject, comprising administering to  
25 the subject a therapeutically effective dose of a pharmaceutical composition

suitable for topical administration to an eye, comprising:

an antibiotic drug in an antibiotic concentration effective for treatment and/or prophylaxis of a gram-positive bacterial infection of at least one tissue of the eye;

5 a pharmaceutically acceptable cyclodextrin compound in a cyclodextrin concentration sufficient to maintain the drug in solution; and

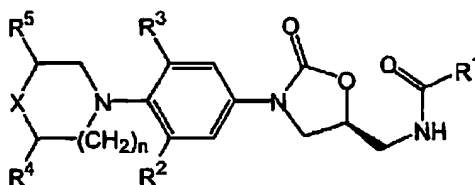
cetyl pyridinium chloride.

20. The method of Claim 19, wherein the subject is a mammal.

21. The method of claim 19, wherein the subject is a human being.

10 22. The method of claim 19, wherein the antibiotic drug is an oxazolidinone antibiotic drug.

23. The method of claim 22 wherein the oxazolidinone antibiotic drug is a compound of formula



15 wherein:

R¹ is selected from (a) H, (b) C<sub>1-8</sub> alkyl optionally substituted with at least one F, Cl, OH, C<sub>1-8</sub> alkoxy, and C<sub>1-8</sub> acyloxy or C<sub>1-8</sub> benzyloxy, including a C<sub>3-6</sub> cycloalkyl group, (c) amino, (d) mono- and di(C<sub>1-8</sub> alkyl)amino and (e) C<sub>1-8</sub> alkoxy groups;

20 R² and R³ are independently selected from H, F and Cl groups;

R⁴ is H or CH<sub>3</sub>;

R⁵ is selected from H, CH<sub>3</sub>, CN, CO<sub>2</sub>R¹ and (CH<sub>2</sub>)<sub>m</sub>R⁶ groups, where R¹ is as defined above, R⁶ is selected from H, OH, OR¹, OCOR¹, NHCOR¹, amino, mono- and di(C<sub>1-8</sub> alkyl)amino groups, and m is 1 or 2;

25 n is 0, 1 or 2; and

X is O, S, SO, SO<sub>2</sub>, SNR⁷ or S(O)NR⁷ where R⁷ is selected from H, C<sub>1-4</sub>



alkyl (optionally substituted with one or more F, Cl, OH, C<sub>1-8</sub> alkoxy, amino, C<sub>1-8</sub> mono- or di(C<sub>1-8</sub> alkyl)amino groups), and p-toluenesulfonyl groups;

or a pharmaceutically acceptable salt thereof.

- 5 24. The method of claim 23 wherein, in said formula, R<sup>1</sup> is CH<sub>3</sub>; R<sup>2</sup> and R<sup>3</sup> are independently selected from H and F but at least one of R<sup>2</sup> and R<sup>3</sup> is F; R<sup>4</sup> and R<sup>5</sup> are each H; n is 1; and X is selected from O, S and SO<sub>2</sub>.
25. The method of claim 22 wherein the oxazolidinone antibiotic drug is selected from the group consisting of: linezolid, eperezolid, N-((5S)-3-(3-  
10 fluoro-4-(4-(2-fluoroethyl)-3-oxopiperazin-1-yl)phenyl)-2-oxooxazolidin-5-ylmethyl)acetamide, (S)-N-[[3-[5-(3-pyridyl)thiophen-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide, (S)-N-[[3-[5-(4-pyridyl)pyrid-2-yl]-2-oxo-5-oxazolidinyl]methyl]acetamide hydrochloride and N-[[[(5S)-3-[4-(1,1-dioxido-  
15 4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.
26. The method of claim 22 wherein the oxazolidinone antibiotic drug is linezolid.
27. The method of claim 26, wherein the pharmaceutical composition is administered in a dose of about 1 to about 100 mg of linezolid at least once per  
20 day.
28. A pharmaceutical composition suitable for topical administration to an eye, comprising:
- (a) linezolid in a concentration effective for treatment and/or prophylaxis of a gram-positive bacterial infection of at least one tissue of the  
25 eye;
- (b) a pharmaceutically acceptable cyclodextrin compound in a

cyclodextrin concentration sufficient to maintain the linezolid in solution; and

(c) cetyl pyridinium chloride.

29. The composition of claim 28 wherein the linezolid concentration is about 0.1 mg/ml to about 100 mg/ml.
- 5 30. The composition of claim 28 wherein the cyclodextrin compound is selected from the group consisting of  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin,  $\gamma$ -cyclodextrin, an alkylcyclodextrin, a hydroxyalkylcyclodextrin, a carboxyalkylcyclodextrin, and sulfoalkylether cyclodextrin.
- 10 31. The composition of claim 28 wherein the cyclodextrin compound is selected from the group consisting of hydroxypropyl - $\beta$ -cyclodextrin and sulfobutylether- $\beta$ -cyclodextrin.
32. The composition of claim 28 wherein the cyclodextrin compound is present at a concentration of about 1 mg/ml to about 500 mg/ml.
33. The composition of claim 28 wherein the cetyl pyridinium chloride is present at a concentration of about 0.001 to about 10 mg/ml.
- 15 34. The composition of claim 28 further comprising an antioxidant.
35. The composition of claim 34 wherein the antioxidant is selected from the group consisting of sodium thiosulfate, acetyl cysteine, cysteine, thioglycerol, sodium sulfite, acetone sodium bisulfite, dithioerythritol, thiourea, and erythrythorbic acid.
- 20 36. The composition of claim 34, wherein the antioxidant is sodium bisulfite.
37. The composition of claim 36, wherein the sodium bisulfite is present at a concentration of about 0.1 to about 5 mg/ml.

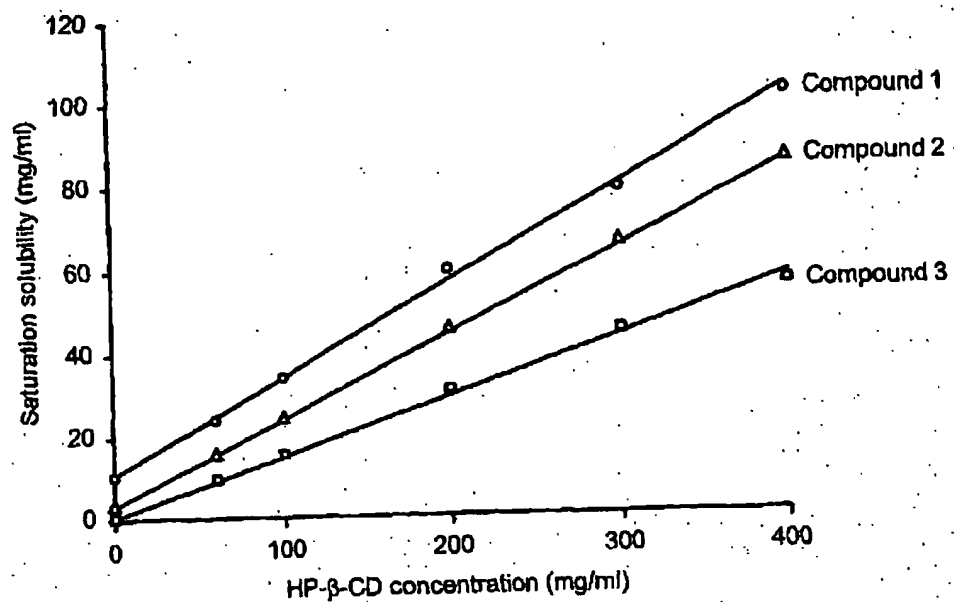


Fig. 1

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/07275

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/40 A61K47/18 A61K31/422 A61P31/04 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 02 05815 A (BANDYOPADHYAY REBANTA ;UPJOHN CO (US); HAWLEY LESLIE C (US); SINGH) 24 January 2002 (2002-01-24)</p> <p>page 1, paragraph 1 page 10, paragraph 30 page 12, paragraph 37 page 14, paragraph 40 page 25, paragraph 65 page 46, paragraph 120 -page 50, paragraph 130</p> <p style="text-align: center;">-/-</p>	<p>1-6,8,9, 12, 15-28, 30,31, 34,36</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

30 June 2003

Date of mailing of the international search report

04/07/2003

Name and mailing address of the ISA

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Houyvet, C

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 03/07275

## C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 97 10805 A (CIBA GEIGY AG ; KIS GYOERGY LAJOS (CH); FETZ ANDREA (CH); SCHOCH CH) 27 March 1997 (1997-03-27) page 1, paragraph 1 page 2, paragraphs 3-5 page 3, paragraphs 2-4 page 4, paragraph 5	1, 8-10, 12-14, 17-21
Y	page 6, paragraph 5 - page 7, paragraph 2 page 8, paragraph 3 - page 9, paragraph 7	1-37
Y	WO 00 03710 A (UPJOHN CO ; COCHRAN ROBERT (US); FORD CHARLES W (US)) 27 January 2000 (2000-01-27) cited in the application page 2, line 5 - page 4, line 2	1-37
Y	WO 00 18387 A (ALCON LAB INC ; CAGLE GERALD (US); STROMAN DAVID W (US); YANNI JOHN) 6 April 2000 (2000-04-06) page 1, line 10-24 page 2, line 18 - page 4, line 15 page 10, line 5 - page 11, line 2	1-37
Y	WO 98 06381 A (ALCON LAB INC ; ESPINO RAMON L (US); CASTILLO ERNESTO J (US)) 19 February 1998 (1998-02-19) page 4, line 4-9 page 5, line 11-17 page 7, line 10, 11	1-37
P, X	WO 02 30395 A (BANDYOPADHYAY REBANTA ; MCCURDY VINCENT E (US); SECREAST PAMELA J) ( ) 18 April 2002 (2002-04-18) the whole document	1-37

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/07275

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 19-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/07275

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Information on patent family members

International Application No

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